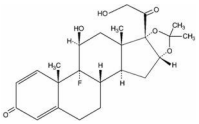
NASACORT - triamcinolone acetonide aerosol, metered
Aventis Pharmaceuticals, Inc.

For Intranasal Use Only
Shake Well Before Using

DESCRIPTION

Triamcinolone acetonide, USP, the active ingredient in **Nasacort**® Nasal Inhaler, is a glucocorticosteroid with a molecular weight of 434.5 and with the chemical designation 9-Fluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone. ($C_{24}H_{31}FO_6$).



Nasacort Nasal Inhaler is a metered-dose aerosol unit containing a microcrystalline suspension of triamcinolone acetonide in dichlorodifluoromethane and dehydrated alcohol USP 0.7% w/w. Each canister contains 15 mg triamcinolone acetonide. Each actuation delivers 55 mcg triamcinolone acetonide from the nasal actuator to the patient (estimated from *in vitro* testing). There are at least 100 actuations in one **Nasacort** Nasal Inhaler canister. **After 100 actuations, the amount delivered per actuation may not be consistent and the unit should be discarded.** Patients are provided with a check-off card to track usage as part of the Information for Patients tear-off sheet.

CLINICAL PHARMACOLOGY

Triamcinolone acetonide is a more potent derivative of triamcinolone. Although triamcinolone itself is approximately one to two times as potent as prednisone in animal models of inflammation, triamcinolone acetonide is approximately 8 times more potent than prednisone.

Although the precise mechanism of corticosteroid antiallergic action is unknown, corticosteroids are very effective. However, they do not have an immediate effect on allergic signs and symptoms. When allergic symptoms are very severe, local treatment with recommended doses (microgram) of any available topical corticosteroids are not as effective as treatment with larger doses (milligram) of oral or parenteral formulations. When corticosteroids are prematurely discontinued, symptoms may not recur for several days.

Based upon intravenous dosing of triamcinolone acetonide phosphate ester, the half-life of triamcinolone acetonide was reported to be 88 minutes. The volume of distribution (Vd) reported was 99.5 L (SD ± 27.5) and clearance was 45.2 L/hour (SD ± 9.1) for triamcinolone acetonide. The plasma half-life of corticosteroids does not correlate well with the biologic half-life.

When administered intranasally to man at 440 mcg/day dose, the peak plasma concentration was <1 ng/mL and occurred on average at 3.4 hours (range 0.5 to 8.0 hours) postdosing. The apparent half-life was 4.0 hours (range 1.0 to 7.0 hours); however, this value probably reflects lingering absorption. Intranasal doses below 440 mcg/day gave sparse data and did not allow for the calculation of meaningful pharmacokinetic parameters.

In animal studies using rats and dogs, three metabolites of triamcinolone acetonide have been identified. They are 6β-hydroxytriamcinolone acetonide, 21-carboxytriamcinolone acetonide and 21-carboxy-6β-hydroxytriamcinolone acetonide. All three metabolites are expected to be substantially less active than the parent compound due to (a) the dependence of anti-inflammatory activity on the presence of a 21-hydroxyl group, (b) the decreased activity observed upon 6-hydroxylation, and (c) the markedly increased water solubility favoring rapid elimination. There appeared to be some quantitative differences in the metabolites among species. No differences were detected in metabolic pattern as a function of route of administration.

CLINICAL TRIALS

In double-blind, parallel, placebo-controlled clinical trials of seasonal and perennial allergic rhinitis, in adults and adolescents in fixed total daily doses of 110, 220 and 440 mcg per day, the responses to aerosolized triamcinolone acetonide demonstrated a statistically significant improvement over placebo. In open label trials where the doses were sometimes adjusted according to patients' signs and symptoms, the daily doses and regimens varied. The most commonly used dose was 110 mcg per day.

Nasacort Nasal Inhaler, at a dose of 220 mcg once daily, has also been studied in two double-blind, placebo-controlled trials of two and four weeks duration in children ages 6 through 11 years with seasonal and perennial allergic rhinitis. These trials included 162 males and 91 females. **Nasacort** administered at a fixed dose of 220 mcg once daily resulted in consistent and statistically significant reductions of allergic rhinitis symptoms over vehicle placebo.

In attempting to determine if systemic absorption played a role in the response to **Nasacort**, a clinical study comparing intranasal and depot intramuscular triamcinolone acetonide was conducted. The doses used were based on bioavailability studies of each formulation. The final doses of **Nasacort** 440 mcg once a day and Kenalog®-40, 4 mg intramuscularly once a week, were chosen to deliver comparable total amounts of weekly triamcinolone acetonide. However, the weekly injection yielded sustained plasma levels throughout the dosing interval while the daily **Nasacort** application resulted in daily peak and trough concentrations, the mean of

which was 3.5 times below the Kenalog plasma levels. Both topical **Nasacort** and intramuscular Kenalog-40 were clinically effective. In addition, in some studies there was evidence of improvement of eye symptoms. This suggests that **Nasacort**, at least to some degree is acting by a systemic mechanism.
In order to evaluate the effects of systemic absorption on the Hypothalamic-Pituitary-Adrenal (HPA) axis, **Nasacort** administered to adults in doses of 440 mcg once a day was compared to placebo and 42 days of a single morning dose of prednisone 10 mg. Adrenal response to a six-hour cosyntropin stimulation test suggests that intranasal **Nasacort** 440 mcg/day for six weeks did not measurably affect adrenal activity. Conversely, oral prednisone at 10 mg/day significantly reduced the response to ACTH.
No evidence of adrenal axis suppression was observed in 26 pediatric patients exposed for 6 weeks to systemic levels of triamcinolone acetonide higher than the systemic levels observed following administration of the maximum recommended dose of **Nasacort** Nasal Inhaler.

INDIVIDUALIZATION OF DOSAGE

Individual patients will experience a variable time to onset and degree of symptom relief when using **Nasacort**. It is recommended that dosing be started at 220 mcg once a day and the effect be assessed in four to seven days.

Adults and Children 12 years of age and older

Some relief can be expected in approximately two-thirds of patients within four to seven days. If greater effect is desired an increase of dose to 440 mcg once a day can be tried. If adequate relief has not been obtained by the third week of **Nasacort** treatment, alternate forms of treatment should be considered.
A dose-response between 110 mcg/day (one spray/nostril/day) and 440 mcg/day (four sprays/nostril/day) is not clearly discernible. In general, in the clinical trials the highest dose tended to provide relief sooner. This suggests an alternative approach to starting therapy with **Nasacort**, *e.g.*, starting treatment with 440 mcg (four sprays/nostril/day) and then, depending on the patient's response, decreasing the dose by one spray per day every four to seven days. Although **Nasacort** may be used at 220 mcg/day or 440 mcg/day divided into two or four times a day, the degree of relief does not seem to be significantly different compared to once-a-day dosing. As with other nasal corticosteroids, the vehicle used to deliver the corticosteroid, may cause symptoms that are difficult to distinguish from the patient's rhinitis symptoms. Thus, depending upon the balance between these vehicle side effects and the benefits of treatment, in determining the optimal dose for the relief of symptoms, individual patients may need to have a trial of high and low doses.

Children 6 through 11 years of age

In children 6 through 11 years of age, it is recommended that dosing be started at 220 mcg given as two sprays (55 mcg/spray) in each nostril once a day. In clinical trials, significant relief of rhinitis symptoms in children was observed as early as the fourth day of treatment and generally, it took one to two weeks to achieve maximum benefit. If adequate relief has not been obtained by the third week of **Nasacort** treatment, alternate forms of treatment should be considered.
In general, it is always desirable to titrate an individual patient to the minimum effective dose to reduce the possibility of side effects. In clinical trials, after symptoms have been brought under control at the recommended starting doses, reducing the daily dose to 110 mcg (one spray in each nostril once per day) has been shown to be effective in controlling symptoms in approximately one-half of adult patients being treated long-term for allergic rhinitis. (See **PRECAUTIONS, WARNINGS, Information for Patients** and **ADVERSE REACTIONS** sections).

INDICATIONS AND USAGE

Nasacort Nasal Inhaler is indicated for the nasal treatment of seasonal and perennial allergic rhinitis symptoms in adults and children 6 years of age and older.

CONTRAINDICATIONS

Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS

The replacement of a systemic corticosteroid with a topical corticoid can be accompanied by signs of adrenal insufficiency and, in addition, some patients may experience symptoms of withdrawal, *e.g.*, joint and/or muscular pain, lassitude and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticoids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.
Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant doses of corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella-zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

The use of **Nasacort** Nasal Inhaler with alternate-day systemic prednisone could increase the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, **Nasacort** Nasal Inhaler should be used with caution in patients already receiving alternate-day prednisone treatment for any disease.

PRECAUTIONS

General

In clinical studies with triamcinolone acetonide administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred. When such an infection develops, it may require treatment with appropriate local therapy and discontinuance of treatment with **Nasacort** Nasal Inhaler.

Triamcinolone acetonide administered intranasally has been shown to be absorbed into the systemic circulation in humans. Patients with active rhinitis showed absorption similar to that found in normal volunteers. **Nasacort** at 440 mcg/day for 42 days did not measurably affect adrenal response to a six hour cosyntropin test. In the same study, prednisone 10 mg/day significantly reduced adrenal response to ACTH over the same period (see **CLINICAL TRIALS** section).

Nasacort Nasal Inhaler should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract or in patients with untreated fungal, bacterial, or systemic viral infections or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing in patients who have experienced recent nasal septal ulcers, nasal surgery or trauma, a corticosteroid should be used with caution until healing has occurred. As with other nasally inhaled corticosteroids, nasal septal perforations have been reported in rare instances.

When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, **Nasacort** Nasal Inhaler should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Information for Patients

Patients being treated with **Nasacort** Nasal Inhaler should receive the following information and instructions.

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

Patients should use **Nasacort** Nasal Inhaler at regular intervals since its effectiveness depends on its regular use. A decrease in symptoms may occur as soon as 12 hours after starting steroid therapy and generally can be expected to occur within a few days of initiating therapy in allergic rhinitis. The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve after three weeks, or if the condition worsens. Nasal irritation and/or burning or stinging after use of the spray occur only rarely with this product. The patient should contact the physician if they occur.

For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying patient instructions carefully. Spraying triamcinolone acetonide directly onto the nasal septum should be avoided. Because the amount dispensed per puff may not be consistent, it is important to shake the canister well. Also, the canister should be discarded after 100 actuations.

Carcinogenesis, Mutagenesis

No evidence of treatment-related carcinogenicity was demonstrated after 2 years of once daily gavage administration of triamcinolone acetonide at doses of 0.05, 0.2 and 1.0 mcg/kg (approximately 0.1, 0.4 and 1.8% of the recommended clinical dose on a mcg/m^2 basis) in the rat and 0.1, 0.6 and 3.0 mcg/kg (approximately 0.1, 0.6 and 3.0% of the recommended clinical dose on a mcg/m^2 basis) in the mouse.

Mutagenesis studies with triamcinolone acetonide have not been conducted.

Impairment of Fertility

No evidence of impaired fertility was demonstrated when oral doses up to 15 mcg/kg (approximately 28% of the recommended clinical dose on a mcg/m^2 basis) were administered to female and male rats. However, triamcinolone acetonide at oral doses of 8.0 mcg/kg (approximately 15.0% of the recommended clinical dose on a mcg/m^2 basis) caused dystocia and prolonged delivery and at oral doses of 5.0 mcg/kg (approximately 9.0% of the recommended clinical dose on a mcg/m^2 basis) and above produced increases in fetal resorptions and stillbirths as well as decreases in pup body weight and survival. At an oral dose of 1.0 mcg/kg (approximately 2.0% of the recommended clinical dose on a mcg/m^2 basis), it did not manifest the above mentioned effects.

Pregnancy

Pregnancy Category C

Triamcinolone acetonide was teratogenic at inhalational doses of 20, 40 and 80 mcg/kg in rats (approximately 0.4, 0.75 and 1.5 times the recommended clinical dose on a mcg/m^2 basis, respectively) and rabbits (approximately 0.75, 1.5 and 3.0 times the recommended

dose on a mcg/m^2 basis, respectively). Triamcinolone acetonide was also teratogenic at an inhalational dose of 500 mcg/kg in monkeys (approximately 18 times the recommended clinical dose on a mcg/m^2 basis). Dose-related teratogenic effects in rats and rabbits included cleft palate, internal hydrocephaly, and axial skeletal defects. Teratogenic effects observed in the monkey were CNS and cranial malformations. There are no adequate and well-controlled studies in pregnant women. Triamcinolone acetonide should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

Experience with oral corticoids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticoids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous steroid dose and many will not need corticoid treatment during pregnancy.

Nonteratogenic Effects
Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers
It is not known whether triamcinolone acetonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when **Nasacort** Nasal Inhaler is administered to nursing women.

Pediatric Use
Safety and effectiveness in pediatric patients below the age of 6 have not been established. Oral corticosteroids have been shown to cause growth suppression in children and teenagers, particularly with higher doses over extended periods. If a child or teenager on any corticosteroid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of steroids should be considered.

ADVERSE REACTIONS

Adults and Children 12 years of age and older
In controlled and uncontrolled studies, 1257 adult and adolescent patients received treatment with intranasal triamcinolone acetonide. Adverse reactions are based on the 567 patients who received a product similar to the marketed **Nasacort** canister.
These patients were treated for an average of 48 days (range 1 to 117 days). The 145 patients enrolled in uncontrolled studies received treatment from 1 to 820 days (average 332 days). The most prevalent adverse experience was headache, being reported by approximately 18% of the patients who received **Nasacort**. Nasal irritation was reported by 2.8% of the patients receiving **Nasacort**. Other nasopharyngeal side effects were reported by fewer than 5% of the patients who received **Nasacort** and included: dry mucous membranes, naso-sinus congestion, throat discomfort, sneezing, and epistaxis. The complaints do not usually interfere with treatment and in the controlled and uncontrolled studies approximately 1% of patients have discontinued because of these nasal adverse effects. In the event of accidental overdose, an increased potential for these adverse experiences may be expected, but systemic adverse experiences are unlikely (see **OVERDOSAGE** section).

Children 6 through 11 years of age
Adverse event data in children 6 through 11 years of age are derived from two controlled clinical trials of two and four weeks duration. In these trials, 127 patients received fixed doses of 220 mcg/day of triamcinolone acetonide for an average of 22 days (range 8 to 33 days).
Adverse events occurring at an incidence of 3% or greater and more common among children treated with 220 mcg triamcinolone acetonide daily than vehicle placebo were:

Adverse Events	**220 mcg of triamcinolone acetonide daily (n=127)**	**Vehicle placebo (n=322)**
Epistaxis	11.0%	9.3%
Cough	9.4%	9.3%
Fever	7.9%	5.6%
Nausea	6.3%	3.1%
Throat discomfort	5.5%	5.3%
Otitis	4.7%	3.7%
Dyspepsia	4.7%	2.2%

Adverse events occurring at a rate of 3% or greater that were more common in the placebo group were upper respiratory tract infection, headache and concurrent infection.

Only 1.6% of patients discontinued due to adverse experiences. No patient discontinued due to a serious adverse event related to **Nasacort** therapy.
Though not observed in controlled clinical trials of **Nasacort** Nasal Inhaler in children, cases of nasal septum perforation among pediatric users have been reported in post-marketing surveillance of this product.

DOSAGE AND ADMINISTRATION

A decrease in symptoms may occur as soon as 12 hours after starting steroid therapy and generally can be expected to occur within a few days of initiating therapy in allergic rhinitis.
If improvement is not evident after 2 to 3 weeks, the patient should be re-evaluated. (See **INDIVIDUALIZATION OF DOSAGE** section).

Adults and Children 12 years of age and older

The recommended starting dose of **Nasacort** Nasal Inhaler is 220 mcg per day given as two sprays (55 mcg/spray) in each nostril once a day. If needed, the dose may be increased to 440 mcg per day (55 mcg/spray) either as once-a-day dosage or divided up to four times a day, *i.e.*, twice a day (two sprays/nostril), or four times a day (one spray/nostril). After the desired effect is obtained, some patients may be maintained on a dose of as little as one spray (55 mcg) in each nostril once a day (total daily dose 110 mcg per day).

Children 6 through 11 years of age

The recommended starting dose of **Nasacort** Nasal Inhaler is 220 mcg per day given as two sprays (55 mcg/spray) in each nostril once a day. Once the maximal effect has been achieved, it is always desirable to titrate the patient to the minimum effective dose.
Nasacort Nasal Inhaler is not recommended for children below 6 years of age since adequate numbers of patients have not been studied in this age group.

Directions for Use

Illustrated Patient's Instructions for use accompany each package of **Nasacort** Nasal Inhaler.

OVERDOSAGE

Acute overdosage with this dosage form is unlikely. The acute topical application of the entire 15 mg of the canister would most likely cause nasal irritation and headache. It would be unlikely to see acute systemic adverse effects even if the entire 15 mg of triamcinolone acetonide was administered intranasally all at once.

HOW SUPPLIED

Nasacort Nasal Inhaler is supplied as an aerosol canister which will provide 100 metered dose actuations. Each actuation delivers 55 mcg triamcinolone acetonide through the nasal actuator. The **Nasacort** Nasal Inhaler canister and accompanying nasal actuator are designed to be used together. The **Nasacort** Nasal Inhaler canister should not be used with other nasal actuators and the supplied nasal actuator should not be used with other products' canisters. **Nasacort** Nasal Inhaler is supplied with a white plastic nasal actuator and patient instructions. Net weight of the canister contents is 10 grams.
NDC 0075-1505-43.

CONTENTS UNDER PRESSURE

Avoid spraying in eyes.
Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Keep out of reach of children. Store at Controlled Room Temperature 20 to 25°C (68 to 77°F) [see USP].
Note: The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFCs):

> WARNING: Contains CFC-12, a substance which harms public health and the environment by destroying ozone in the upper atmosphere.

A notice similar to the above WARNING has been placed in the "Information For The Patient" portion of this package insert under the Environmental Protection Agency's (EPA's) regulations. The patient's warning states that the patient should consult his or her physician if there are questions about alternatives.

U.S. Pat. No. 4,767,612

Manufactured by:
Armstrong Pharmaceuticals, Inc.
West Roxbury, MA 02132 USA
Manufactured for:
Aventis Pharmaceuticals Inc.
Bridgewater, NJ 08807 USA

Prescribing Information as of January 2002
IN-0479J

INFORMATION FOR THE PATIENT

Using your

Nasacort®
(triamcinolone acetonide)

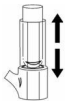
Nasal Inhaler

IMPORTANT: Please read these instructions carefully before using your **Nasacort®** Nasal Inhaler.

Before each use of your **Nasacort®** Nasal Inhaler, gently blow your nose, making sure your nostrils are clear. Then follow these steps:

Step 1
Remove the white protective cap from the nasal inhaler.

Step 2
Shake the canister well.



Step 3
Hold the inhaler between your thumb and forefinger.

Step 4
Tilt your head back slightly and insert the end of the inhaler into one nostril, pointing it slightly toward the outside nostril wall away from the nasal septum, while holding your other nostril closed with one finger.

Step 5
Press down on the canister to release one spray and, at the same time, inhale gently.

Step 6
Hold your breath for a few seconds, then breathe out slowly through your mouth.

Step 7
Withdraw the nasal inhaler from your nostril.

Step 8
Repeat the process in your other nostril.

NOTE: When the physician prescribes more than one spray per nostril, for each spray repeat steps 4 through 8.

Step 9
Replace the white protective inhaler cap on the nasal inhaler.

NOTE: AVOID BLOWING YOUR NOSE FOR THE NEXT 15 MINUTES.

DOSAGE: Use only as directed by your physician.

Your **Nasacort®** Nasal Inhaler should be cleaned weekly. Remove the white protective cap from nasal inhaler. Remove the canister from the nasal inhaler. Clean the nasal inhaler *thoroughly* in lukewarm water. The use of soap, detergent, or disinfectant is not

necessary. Allow the inhaler to *dry completely.* Gently center and insert the canister with the plastic stem downward into the small hole at the bottom of the nasal inhaler. Replace the white protective cap on nasal inhaler. The canister should be discarded after 100 actuations. The canister and nose piece are designed to be used together. Never use this canister or nose piece with those from any other product.

NOTE: Nasacort® Nasal Inhaler is not intended to give immediate relief of your nasal symptoms. Your particular symptoms may require regular use of this drug for a few days or more before improvement. Therefore, it is important that you use the **Nasacort®** Nasal Inhaler regularly as recommended by your physician.

CAUTION: Contents under pressure. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator.

Keep out of reach of children.

Store at Controlled Room Temperature 20 to 25°C (68 to 77°F) [see USP].

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How to check contents of your Nasacort® Nasal Inhaler

Shaking your canister will NOT give you a good estimate of how much is left.

We have included a convenient check-off chart to assist you in keeping track of medication sprays used. This will help assure that you receive the 100 "Full Sprays" of medication present.

- Retain with medication or affix to convenient location.
- Starting with spray #1, check off after each use.
- **DISCARD MEDICATION AFTER 100 SPRAYS.**

Note: The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFCs):

This product contains CFC-12, a substance which harms the environment by destroying ozone in the upper atmosphere.

Your physician has determined that this product is likely to help your personal health. **USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR PHYSICIAN.** If you have any questions about alternatives, consult with your physician.